Case report

Contact urticaria syndrome caused by haptens

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Abstract

In the group of urticaria, contact urticaria syndrome is a particular variety. In these patients, appearance of typical skin lesions is preceded by contact of the skin and mucous membranes with various inhaled allergens, nutrients or contact details. Furthermore, symptoms connected with contact urticaria syndrome are characterized by gradual, stepwise waveform, which can be easily generalized – patients may develop systemic symptoms similar to those found in the angioedema, asthma or anaphylactic shock. It is an attribute of contact urticaria syndrome in the course of which potentially life-threatening symptoms may develop after contact of the skin with the allergen. The underlying mechanisms are poorly understood; both immunological and non-immunological mechanisms are taken into account, therefore contact urticaria syndrome can be classified into two categories – allergic and non-allergic. An intriguing phenomenon seems to be the immediate reaction after exposure to low molecular weight allergens – haptens, such as metals, which are usually the cause of delayed allergic reactions. Diagnosis is based on clinical presentation indicating a coincidence of the onset of allergy with contract with allergen, and helpful exposure tests. Treatment consists of supportive antihistamines and corticosteroids – locally and systemically. In the case of anaphylaxis, appropriate treatment intensification of the integration of pressor amines and hydration is necessary. It is also regarded that prevention is advisable, which consists of relevant information to avoid situations connected with contact with well-known factors. In this paper we describe a case of a 57-year-old female admitted to the Department of Internal Medicine, Geriatrics and Allergology, Medical University in Wroclaw to undergo diagnostic tests of chronic urticaria and angioedema. According to information obtained from the clinical presentation and after the diagnostic procedures, contact urticaria syndrome due to exposure to metals was diagnosed.

Key words: contact urticaria syndrome, haptens, immediate contact reaction.

Introduction

Contact urticaria syndrome is one of the forms of the urticaria with a variety of symptoms – local and systemic which can occur in many clinical forms of contact urticaria, but it is most common in patients with allergic urticaria. Contact urticaria syndrome was defined by Maibach and Johnson in 1975 [1]. Since then, numerous reports of contact urticaria syndrome caused by a variety of compounds, such as foods, preservatives, metals, plant and animal allergens, have been presented [2, 3]. One study of patients with urticaria found that contact urticaria constituted an estimated 1.1% of all urticaria cases at the facility [4–6]. Because exposure to causal agents for contact urticaria can be similar to exposure to contact irritants, vigilance is required to ensure that the patient is properly investigated and diagnosed. Contact urticaria syndrome can be divided in two categories: non-immunologic contact urticaria and immunologic contact urticaria [7–9]. However, the precise mechanisms by which both immunologic and non-immunologic urticaria are elicited remain poorly defined. Non-immunologic contact urticaria is thought to be caused by the direct release of vasoactive substances from cells, especially by granulocytes. Some of more commonly reported causes of non-immunologic contact urticaria include ingredients of cosmetics and medicaments (i.e. balsam of Peru, benzoic acid, cinnamic alcohol, cinnamic aldehyde – cosmetic intolerance syndrome) [10], sorbic acid (preservative used in many foods), dimethyl sulfoxide (DMSO), metals (cobalt chloride, nickel sulfate, palladium), raw meat, fish and vegetables (oral allergy syndrome). For instance, immunologic contact urticaria reactions are considered immediate IgE-mediated reactions that may spread beyond the site of contact and progress to generalized urticaria or even, when more severe, may lead to anaphylactic shock. This can happen, for example, as

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a result of contact with not only natural rubber latex (e.g. surgical gloves), phenylmercuric propionate, many antibiotics, parabens, salicylic acid, polyethylene glycol, short chain alcohols, but also raw meat, fish and vegetables [11–18]. However, some contact urticaria reactions of unknown mechanism are unclassified and could be associated with generalized histamine-type reactions. Contact urticaria syndrome in its clinical course is characterized by a sequence of local and systemic symptoms, so for the relevant diagnosis of this syndrome the coincidence of skin changes – urticaria and systemic symptoms is necessary. Symptoms may develop at the first exposure to the inducing substance and usually are limited to the site of contact. Amin and Maibach described the staging system for contact urticaria syndrome [1, 6]. In this classification, stage 1 is associated with localized urticaria (redness and swelling), dermatitis (eczema) and some nonspecific symptoms (e.g. itching, tingling, burning sensation). Stage 2 was described as generalized urticaria. Patients presenting stage 3 of contact urticaria syndrome may present symptoms of bronchial asthma (dyspnea, wheezing), angioedema, rhinitis, conjunctivitis (running nose, watery eyes), oropharyngeal symptoms (e.g. lip swelling, hoarseness, difficulty in swallowing), gastro-intestinal symptoms (nausea, vomiting, diarrhea, cramps). Stage 4 in the course of contact urticaria syndrome is connected with generalized anaphylactic reactions, including anaphylactic shock. According to the above classification, stages 1 and 2 are characterized only by cutaneous reactions, while stages 3 and 4 demonstrate extracutaneous and systemic reactions. Treatment of this syndrome includes the use of local and general antihistamines and local corticosteroids. Antibiotics should be also considered especially when bacterial superinfection symptoms developed. General symptoms of anaphylaxis require treatment intensification, including parenteral administration of epinephrine, antihistamines and systemic corticosteroids. The prognosis in contact urticaria syndrome is entirely dependent on the ability of the patient to avoid etiologic substances. However, even in cases of severe immunologic contact urticaria, the long-term prognosis can be good if patients take an active role in controlling their environment by educating themselves and others and by taking all proper precautions [5, 8].

Case report

A 57-year-old female with medical co-morbidities (i.e. hypertension, nonallergic bronchial asthma) and without the chronic allergic family history, was admitted on 16 October 2011 to the Department of Internal Diseases, Geriatrics and Allergology, Medical University of Wroclaw, Poland to undergo diagnostic tests because of incidents of recurrent urticaria and angioedema (Figure 1). Accord-

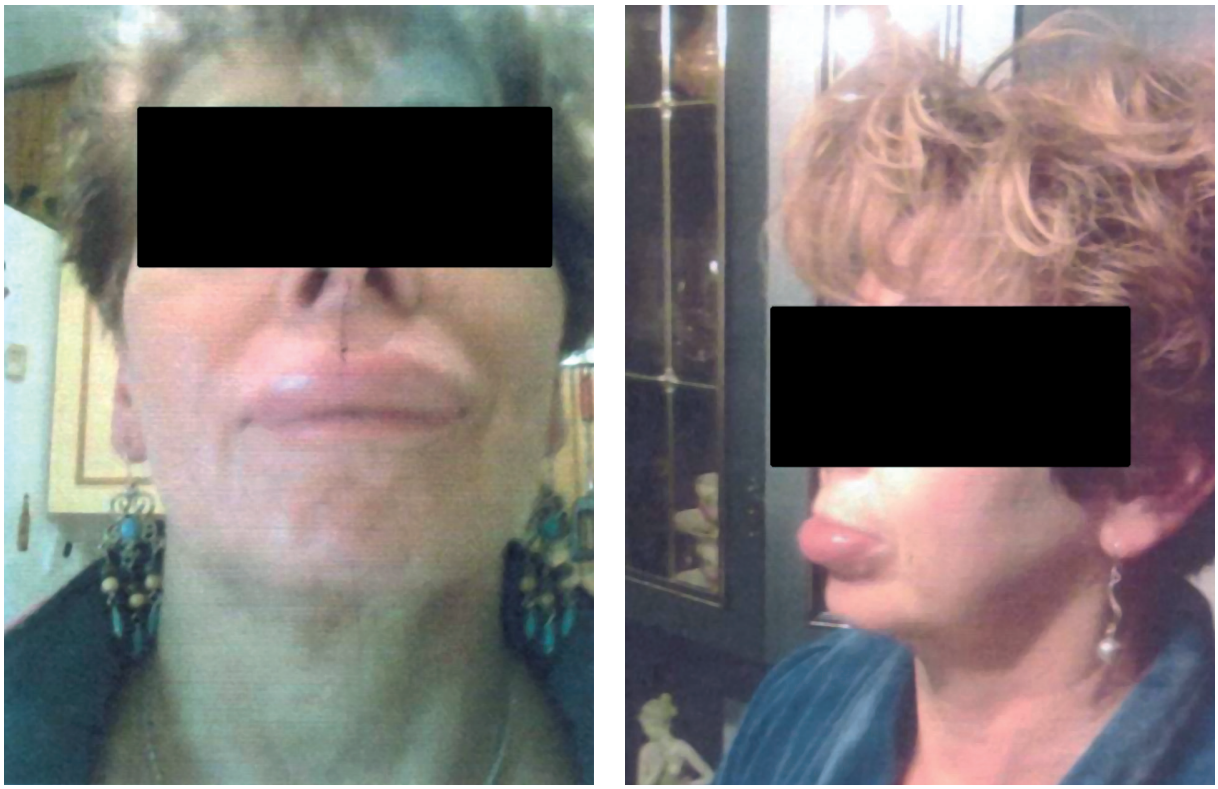

Figure 1. Angioedema of the lips in the presented patient

ing to the history provided by the patient, symptoms have been present for several years without any clear relation to the inhaled or nutritional agents or drugs and were not accompanied by any difficulties in breathing but could be connected with contact with necklaces, earrings and trouser belt buckle. Angioedema occurred within the face and urticaria, skin changes covered many areas of the body (usually the upper limbs and trunk) especially those being in contact with metal items. On admission, the patient was in a good and stable condition. Physical examination showed no significant deviations from the normal condition and there were no changes of urticaria or angioedema. Blood counts revealed normal white blood count (WBC) and platelet (PLT) counts and no eosinophilia (WBC 8.14 thousand/µl, PLT 308 thousand/µl, eosinophils 0.67 thousand/µl); blood coagulation parameters were normal (APTT 25.4 s, INR 0.93). There was no increase in the concentration of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (3.7 mg/l and 21 mm at 1 h, respectively). No abnormalities in the biochemical activity of liver enzymes were observed: aspartate aminotransferase (AST 18 U/l), alanine aminotransferase (ALT 18 U/l), γ-glutamyl transferase (GGT 40 U/l), alkaline phosphatase (AP 58 U/l). Renal parameters were normal (urea 18 mg/dl, creatinine 0.64 mg/dl, eGFR 101.66 ml/min). Urinalysis revealed microscopically no major deviations from the normal state. Examination of feces for the presence of worm's eggs came out negative. An assessment of the complement system revealed no abnormalities (C3 1.29 g/l and C4 0.26 g/l). C1-esterase inhibitor concentration was within normal limits (0.3 g/l). Total IgE levels were slightly elevated (130 IU/ml at standard to 100 IU/ml). Investigations for connective tissue diseases and autoimmune diseases (ANA, p-ANCA, cANCA, anticardiolipin antibodies) were all negative and rheumatoid factor was undetectable. Thyroid function was normal and anti-TG and anti-TPO were not elevated. Investigations for hepatitis B and C were negative. The rub test in the direction of dermographism was negative. In the course of further diagnostic tests, the prick-tests with ubiquitous inhalant and nutritional allergens were performed and gave no positive results. The compression test and the thermal exposure test with high and low temperature apparently gave negative results. Oral provocation test with acetylsalicylic acid to the total cumulative dose of 600 mg was negative. Skin patch tests gave strong positive reactions with palladium, benzocaine and nickel sulfate after 72 h of contact (Figure 2). The patient's clinical condition remained stable. Therefore, taking into account the information obtained from the clinical presentation and the overall diagnostic studies, the occurrence of incidents of urticaria and angioedema in a patient without evidence of atopy was associated with exposure to metals.

Discussion

Skin eruptions of the type of urticaria are considered to be one of the most common diseases of the skin layers – it is estimated that they may affect even about 3% of the adult population and have a significantly negative impact on the quality of life of patients [19–22]. This group of skin lesions includes the contact urticaria syndrome – this term was used for the first time in the literature in 1975 by Maibach *et al.*, and the frequency of its occurrence in accordance with literature data is estimated to be approximately 1–2% of all patients with urticaria [1, 4, 23, 24]. The majority of adult patients recover quickly, especially with appropriate treatment and after discontinuation of the contact with the causative agent; there are also reports of cases of this syndrome among younger population [6, 9, 25]. Contact urticaria syndrome is one of the forms of the immediate bubble-edematous response caused by direct contact of the skin with the inducing substance. The clinical manifestation is here dominated by the diverse local changes limited to the

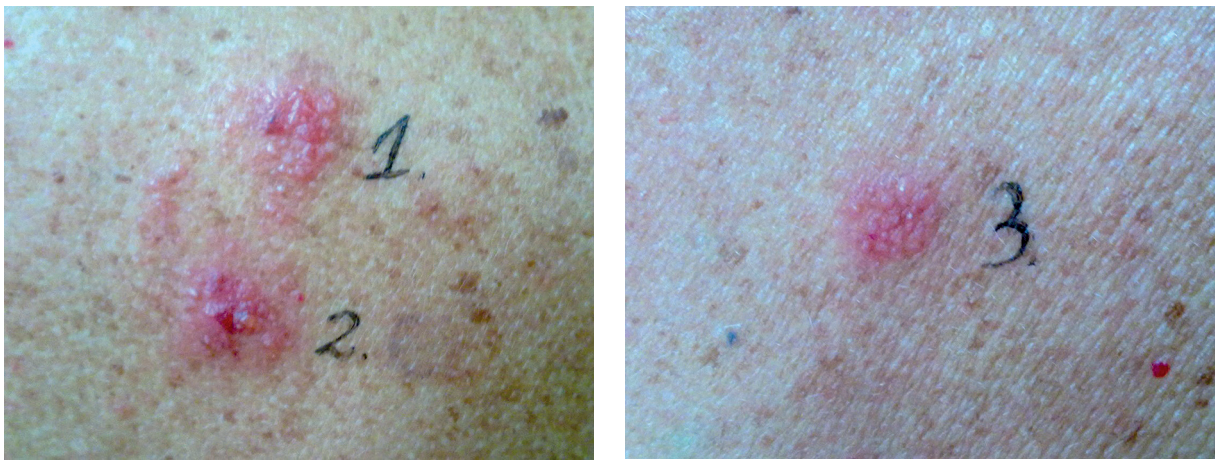

Figure 2. Positive reactions to palladium (1), benzocaine (2) and nickel sulfate (3) after 72 h of contact in skin patch tests

contact area. The mildest symptoms suggesting this syndrome include itching, tingling and redness at the place of contact, then typical changes specific to urticaria as bubbles and blisters caused by effusion can be observed [4, 9, 26]. These changes may, in turn, be accompanied by symptoms from other systems and organs, what is consistent with the definition of contact urticaria syndrome. The nasal symptoms, generalized angioedema, conjunctivitis, bronchospasm, dyspepsia, debilitation, fever or even full-blown anaphylactic shock can be observed. Due to the presence of antigen presenting cells, lymphocytes and keratinocytes, the skin is susceptible to elicit various symptoms of hypersensitivity and allergic symptoms. What is more, the main pathophysiological factor in the syndrome described above is the disturbance in the microcirculation within the skin, which is formed during the ongoing immunological or non-immunological response under the impact of mediators. In view of the possible pathomechanisms, contact urticaria syndrome being caused by many factors, may be divided e.g. to the allergic, non-allergic, and even idiopathic and symptomatic variants [4, 5, 7, 27]. In order to identify a potential etiologic factor causing contact urticaria syndrome, the diagnosis should be based on data obtained from the interview and physical examination, and then it needs to be objectified by skin prick tests, skin patch tests (including metals, substrates for ointments and cosmetics), provocation tests with low and high temperature, compression test, test with autologous serum, as well as provocation tests in cases suspected of being allergy to drugs or cosmetics [5, 25, 28–30]. It should be recognized that in the clinical case described above, the criteria for contact urticaria syndrome caused by low molecular weight allergens – haptens, which include metals, have been fulfilled. The patient experienced typical symptoms of this syndrome – appearance of skin lesions of the type of urticaria involving many areas of the body and then angioedema located on the face. Moreover, the aspect of the symptoms' onset after skin contact with metal parts of clothing and jewelry while other causative factors were absent is characteristic and seems to confirm the existence of the cause-and-effect relationship to the exposure to heavy metals. In this case, it was pivotal to perform skin patch tests with various contact allergens applied to the skin of the patient's back, what allowed to establish the diagnosis of contact urticaria syndrome associated with metals (palladium, nickel), which are known as one of the factors responsible for the occurrence of this syndrome, especially on non-immunologic grounds. Analyzing further the presented case, it should be noted that based on research conducted in our unit during the differential diagnosis of other diseases with cutaneous manifestations, the following were excluded, including among others systemic connective tissue disease, rheumatoid arthritis, inflammatory viral hepatitis, autoimmune thyroiditis, a parasitic infestation of the gastrointestinal tract, hereditary angioedema and urticaria caused by high and low temperature or pressure. Due to the recurrent nature of possible skin changes, the patient was given detailed information on the potential factors determining the appearance of urticarial eruptions and angioedema and she was advised to avoid them (especially avoid contact with metal parts made of nickel and palladium). Temporarily, in a situation of acute and massive seeding urticarial and angioedematous changes, the use of oral corticosteroids and antihistamines and also immediate medical evaluation on an outpatient basis are recommended.

Conflict of interest

All authors declare no conflict of interest.

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